REMARKS

Claims 1, 3, 4, 8-13, 15-43, 45-50, 55-60, and 63-66 are pending in this application.

Applicants gratefully acknowledge the withdrawal of the finality of the Office Action dated March 17, 2009.

I. The Rejection Under 35 U.S.C. § 112, first paragraph Should be Withdrawn

Claims 1, 3, 8-13, 17, 18, 31-35, 45-50, 55, 63, and 66 stand rejected under 35 U.S.C. 112, first paragraph. The Office contends that "the specification, while being enabling for [a number of] organic solvents … [the specification] does not reasonably provide enablement for all organic solvents." (emphasis added)

The Office's requirement that the specification be enabling for all organic solvents is improper because it is inconsistent with the teachings of the specification. The specification teaches that the claimed compositions are administered to humans in the treatment of particular diseases or disorders. It is well known in the pharmaceutical arts that not all organic solvents are acceptable or approved for administration to humans. Thus, the broadest reasonable interpretation of the claims that is also consistent with the specification would not embrace all organic solvents as contended by the Office.

Applicants respectfully submit that the test of enablement is met in the present application at least because the specification is (1) enabled for a number of organic solvents (as acknowledged by the Office) and (2) the specification provides sufficient guidance to one skilled in the art with regard to selecting organic solvents for use in the claimed invention.

The analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. MPEP § 2164.01 The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use

the full scope of the claimed invention without 'undue experimentation'." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed in the specification. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (emphasis added). When analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification. MPEP § 2164.08 (emphasis added). See also MPEP § 2111 which states that the broadest reasonable interpretation standard is the "broadest reasonable construction [of the claims] in light of the specification as it would be interpreted by one of ordinary skill in the art." Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005)(quoting In re Am. Acad. of Sci. Tech. Ctr., 367 F.3d 1359, 1364, 70 USPQ2d 1827 (Fed. Cir. 2004)). In sum, all that is necessary for enablement is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. MPEP § 2164.08

As a threshold matter, the Office's determination that "the claims are broad requiring that the modafinil be soluble or dissolve in all organic solvents" is improper because it is inconsistent with the teachings of the specification. (See Office Action, page 4, line 1)(emphasis added). The specification describes embodiments in which the claimed particle-forming compositions are administered to a subject, such as a human or human child. (See page 5, lines 13 – 15, for the definition of "subject"). It is well known in the pharmaceutical arts that not all organic solvents are acceptable or approved for administration to humans.

The application also describes that the compositions of the invention are suitable for oral administration, (See, for example, page 13, lines 26 – 32) and that the claimed compositions are "useful in the treatment of sleepiness, such as excessive daytime sleepiness associated with narcolepsy, or sleepiness associated with sleep apneas". (See, for example, page 12, lines 11 – 17).

Thus, the broadest reasonable interpretation of the claims that is also consistent with the specification would not embrace all organic solvents as contended by the Office. One of skill in the art reading the present application would readily understand that the claimed compositions were intended for human use and therefore the claimed compositions would comprise organic solvents that are acceptable or approved for administration to humans. Accordingly, undue experimentation is not required for one skilled in the art to use or practice the claimed invention.

This is not to say that the application must enable all of the organic solvents approved for human use. It is well established that "not everything necessary to practice the invention need be disclosed." In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

As acknowledged by the Office, the present application is enabled for a number of organic solvents including, *inter alia*, glycerin, propylene glycol, diethylene glycol ethyl ether, polyethylene glycols, and others. (See, for example, page 8, line 22 through page 9, line 12). The specification also provides explicit guidance to one of skill in the art on selecting organic solvents suitable for use in the claimed invention, i.e., "an appropriate organic solvent is one which increases the solubility of a modafinil compound in a particle-forming composition and does not adversely impact upon the formation of suspended particles." (See page 8, lines 28-30). The specification also describes additional organic solvents, such as alkyl alcohols and alkylaryl alcohols, in embodiments comprising mixtures of organic solvents. (See, for example, page 9, lines 19 – 24). The specification also provides a number of working examples on pages 18 through 20.

For at least all of the reasons set forth above, the scope of the pending claims is enabled because the skilled artisan, appropriately guided by the specification and the knowledge in the art, would not have to carry out undue experimentation to practice or use the claimed invention.

II. The Rejections Under 35 U.S.C. § 103 are Improper and Should be Withdrawn

Claims 1, 3, 4, 8-13, 15, 17-35, 45-47, 55, 59, 63, and 66 stand rejected as allegedly unpatentable over Nguyen et al. (US 5,843,347; hereinafter US '347) in view of Esteve et al. (US 6,566,404; hereinafter US '404) and Grebow et al. (US 5,618,845; hereinafter US '845) and in further view of Santus et al. (US 5,510,119; hereinafter US '119).

Claims 1, 3, 4, 8-13, 15, 17-35, 45-50, 55, 59, 63, and 66 rejected as allegedly unpatentable over Nguyen et al. (US 5,843,347; hereinafter US '347) in view of Grebow et al. (US 5,618,845; hereinafter US '845) and in further view of Santus et al. (US 5,510,119; hereinafter US '119).

The Office has failed to establish a *prima facie* case of obviousness against the pending claims at least because the primary reference, i.e. US '347, "teaches away" from the claimed invention. A reference that teaches away from the claimed invention cannot support a *prima facie* case of obviousness. See MPEP § 2145 X.D. The rejection is therefore improper for at least this reason and should be withdrawn.

In the alternative, assuming *in arguendo* that US '347 is not found to "teach away" from the claims, the Office has still failed to establish a *prima facie* case of obviousness at least because (1) the references alone or in combination fail to teach or suggest all of the elements of the pending claims; and (2) the Office has not shown that one of ordinary skill in the art would have been motivated to modify the teachings of US '347 in view of the other references so as to arrive at the claimed invention. The rejections are improper for at least these additional reasons and should be withdrawn.

US '347 teaches away from the claims

The Office is well aware that "[i]t is improper to combine references where the references teach away from their combination." In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983) (The claimed catalyst which contained both iron and an alkali metal was not suggested by the combination of a reference which taught the interchangeability of antimony and alkali metal with the same beneficial result, and another reference that added iron to a catalyst but expressly excluded antimony). See also, In re Gurley, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130 (Fed. Cir. 1994)(agreeing that "a reference that "teaches away" can not serve to create a prima facie case of obviousness" is a useful general rule).

A reference is said to "teach away" when one of ordinary skill in the art, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994)(emphasis added).

As discussed below, US '347 teaches away from the claimed composition and from its combination with the other cited references. In particular, US '347 teaches away from the claims at least because US '347 teaches a **dry** particle made by a process that initially **requires the presence of water**. In view of the non-aqueous liquid solution of the present claims, one of ordinary skill in the art reading US '347 would be led in a direction divergent from the path taken by the Applicants.

US '347 teaches a process that "comprises the production of **dry cores** of regular shape, preferably of spherical shape, by extrusion or forming and then lyophilization". (US '347, Col. 4, lines 16-19)(emphasis added). More specifically, US '347 teaches an initial process step "consisting of (1.) the preparation of a homogeneous mixture from (a) at least one active ingredient, (b) a physiologically acceptable hydrophilic excipient, and (c) **water** to give a pasty mixture with a viscosity below 1 Pa.s, measured at room temperature (15° -20° C)…" (US '347, Col 5, lines 2-8)(emphasis added). The aqueous homogeneous mixture is extruded

and the extrudate cut to provide moist (wet) particles, which are subsequently dried in the last step of the process. (US '347, Col 5, lines 9-15)

To contrast, the pending claims are directed to, *inter alia*:

> A **non-aqueous**, **liquid solution** comprising a modafinil compound . . . characterized in that the solution **spontaneously forms** an aqueous, liquid, homogeneous, stable **composition of non-crystalline particles when contacted with an aqueous medium**. (emphasis added)

The specification expressly states that "[i]t is desirable to formulate modafinil in liquid formulations." (page 2, lines 10-11). The non-aqueous, liquid solution of the pending claims is directly opposed to and is irreconcilable with the **dry particles** taught in US '347.

In rejecting the pending claims, however, the Office selected specific elements of the US '347 disclosure and applied the elements to the pending claims in isolation and without context. In doing so, the Office has failed to view the invention and each reference as a whole as is required. MPEP § 2141.02 Moreover, this piecemeal view of US '347 obscures the fact that US '347 clearly teaches away from the claims.

The non-aqueous, liquid solution of the claims cannot be reconciled with the initial process step taught in US '347 in which "[a]fter homogenization, the active ingredient is in the form of a solution, suspension or emulsion" at least because US '347 expressly teaches that the homogenized mixture is aqueous. Nor can pending claims be reconciled with US '347 teaching a dry, i.e. non-aqueous, particle as the penultimate outcome of the process because the pending claims provide for a liquid solution.

"In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." Stratoflex, Inc. v. Aeroquip

Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); Schenck v. Nortron Corp., 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983)(emphasis added).

Viewing US '347 and the claimed invention as a whole, as is required, the non-aqueous liquid solution provided by the present claims is clearly a marked departure from the teachings of US '347. As such, US '347 teaches away from the claims because one of ordinary skill in the art reading US '347 would have been led in a direction divergent from the path taken by the Applicants. Thus, the rejections based on US '347 as a primary reference are improper for at least this reason.

The Office has failed to establish a *prima facie* case of obviousness

In the alternative, assuming *in arguendo* that US '347 is not found to "teach away" from the claims, the Office has still failed to establish a *prima facie* case of obviousness. No *prima facie* case has been established at least because: (1) the references taken alone or in combination fail to teach or suggest every element of the claims; and/or (2) the Office has not shown that one of ordinary skill in the art would have been motivated to modify the teachings of US '347 in view of the other references so as to arrive at the claimed invention.

In its efforts to try to establish a *prima facie* case, the Office has engaged in impermissible hindsight, piecing together selected teachings from each of the references using Applicants' specification as a blueprint. This is in direct contrast to the MPEP and case law which requires that any judgment on obviousness must "not include knowledge gleaned only from applicant's disclosure." See In re McLaughlin, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971).

As discussed above, US '347 teaches a process for making dry particles via extrusion of a homogenous aqueous mixture which is subsequently lyophilized. The Office relies on US '404 as allegedly disclosing liquid formulations of modafinil. The Office relies on US '845 as

teaching modafinil formulated as a suspension or emulsion. The Office further relies on US '119 as teaching that liquid formulations are better accepted by patients.

As discussed above US '347 does not teach the **non-aqueous liquid** solution of modafinil of the present claims. Moreover, taking the teachings of the references together in view of US '347 still does not teach all of the elements of the present claims as suggested by the Office. Further the Office fails to supply a reason why one of ordinary skill in the art would be motivated to combine the teachings of the references so as to arrive at the claimed invention.

The cited references, US '404, US '845, and US '119, whether viewed alone or in combination, all fail to teach or suggest a non-aqueous liquid solution of modafinil. Thus, these references suffer the same deficiencies as US '347. Moreover there is no motivation to combine US '347 with these additional references so as arrive at the claimed invention.

In particular, US '404 fails to disclose a non-aqueous liquid formulation of modafinil. Rather, in Col. 2, lines 9-22, US '404 teaches that modafinil may be administered as a medicament "in the form of gelatine capsules, tablets, coated tablets, capsules and analogous products." At best, US '404 teaches that modafinil may be administered via injection where such injectable formulations are "in the form of solutions". However, this general description does not teach or suggest the **non-aqueous** liquid solution of the present claims at least because most injectable formulations are aqueous. See, for example, Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th edition, page 403 (stating that "The most frequently used solvent in the large scale manufacture of injection is *Water for Injection, USP*)(enclosed with this Response).

US '845 also fails to teach or suggest the elements of the claims that are missing from US '347 and US '404. In particular, US '845 teaches an **aqueous** suspension of modafinil an

(US '845, Col. 8, lines 22-37). Again, this is not the non-aqueous liquid solution of the present claims.

Finally, US '119 also fails to teach or suggest the elements of the claims missing from the disclosures of the other references. In particular, US '119 teaches a controlled release aqueous liquid formulations of coated microgranules of a pharmaceutical, namely theophylline.

For all of the reasons outlined above, the Office has failed to establish a *prima facie* case of obviousness. The various rejections as applied to all pending claims are therefore improper and should be withdrawn.

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Claims 1, 3, 4, 8-13, 15, 17-35, 45-47, 55, 59, 63, and 66 also stand rejected as allegedly unpatentable over US '347 in view of Shah et al. or Charman et al.

Claims 48-50 stand rejected as allegedly unpatentable over US '347 in view of Shah et al.

Claims 1, 15 and 16 stand rejected as allegedly unpatentable over US '347 in view of US '845 and US '119 in further view of Hochlowski (US 5,589,485; hereinafter US '485)

The Office has failed to establish a *prima facie* case of obviousness

Assuming *in arguendo* that US '347 is not found to "teach away" from the claims, the Office has still failed to establish a *prima facie* case of obviousness. No *prima facie* case has been established at least because: (1) the references taken alone or in combination fail to teach or suggest every element of the claims; and/or (2) the Office has not shown that one of ordinary skill in the art would have been motivated to modify the teachings of US '347 in view of the other references so as to arrive at the claimed invention.

In its efforts to try to establish a *prima facie* case, the Office has engaged in impermissible hindsight, piecing together selected teachings from each of the references using Applicants' specification as a blueprint. This is in direct contrast to the MPEP and case law which requires that any judgment on obviousness must "not include knowledge gleaned only from applicant's disclosure." See In re McLaughlin, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971).

The discussions of the deficiencies of US '347, US '845, and US '119 set forth above apply equally to the rejections founded on the combinations with Shah et al., Charman et al., and US '485. However, the additional references, Shah et al., Charman et al. and US '485, all suffer the same deficiencies as US '347, US '845, and US '119 because none of the additional references teach or suggest the elements of the pending claims that are missing from the disclosures of the aforementioned references. Moreover, there is no motivation for one of ordinary skill in the art to combine the teachings of the references so as to arrive at the claimed invention.

As discussed above, US '347 fails to disclose the non-aqueous liquid formulation of the pending claims. As discussed in previous responses, Shah et al. and Charman et al. are both directed toward the delivery of **lipophilic compounds** (Shah at page 15; Charman at page 87). Because modafinil is **poorly soluble** in lipids, one of ordinary skill in the art would have no motivation to modify US '347 with the teachings of Shah et al. or Charman et al. at least because both Shah and Charman are directed toward the delivery of compounds with solubility characteristics exactly **opposite** those of modafinil. *See* MPEP § 2143.02.II (no *prima facie* case of obviousness where no expectation that prior art would successfully arrive at claimed invention). For this reason, the combination of US '347 with Shah et al. and/or Charman et al. cannot support a *prima facie* case of obviousness.

Further, even if combining US '347 with Shah et al. or Charman et al. were proper, the resulting composition would not address every element of the pending claims at least because the claimed compositions include, *inter alia*, modafinil, which is – as discussed – **poorly**

soluble in lipids. Accordingly, the proposed combination cannot support a *prima facie* case of obviousness. *See* MPEP § 2143.03 (prior art must address all elements of claim in order to make out *prima facie* case of obviousness).

Finally, US '485 also fails to teach or suggest the claim elements missing from US '347, US '845, and US '119. Specifically, US '485 fails to teach or suggest the non-aqueous liquid solution of modafinil of the present claims.

US '485 is directed to glutarimide compounds isolated from the microorganism, *Streptomyces*, and pharmaceutical compositions comprising these compounds. In rejecting the present claims, the Office relies on US '485 as teaching "the further presence of solvents such as benzyl alcohol" and not to support the rejection of claim 1. As such the Office has not relied on US '485 as teaching "a non-aqueous liquid solution." (See Action, paragraph 29, page 18). Because US '347, US '845, US '119, and US '485 all fail to teach or suggest the non-aqueous liquid solution of modafinil of the pending claims, the Office, by its own admission, has failed to establish a *prima facie* case of obviousness.

For all of the reasons outlined above, the Office has failed to establish a *prima facie* case of obviousness. The various rejections as applied to all pending claims are therefore improper and should be withdrawn.

CONCLUSION

For at least the reasons set forth herein, Applicants respectfully submit that each rejection and objection has been addressed. It is believed that the pending claims are in form for allowance, and an early notification to that end is respectfully requested. Applicants invite the Examiner to contact the undersigned at (610) 727-6328 to clarify any remaining issues.

Respectfully submitted,

/ Rona A. Nardone /

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SEVENTH EDITION

PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

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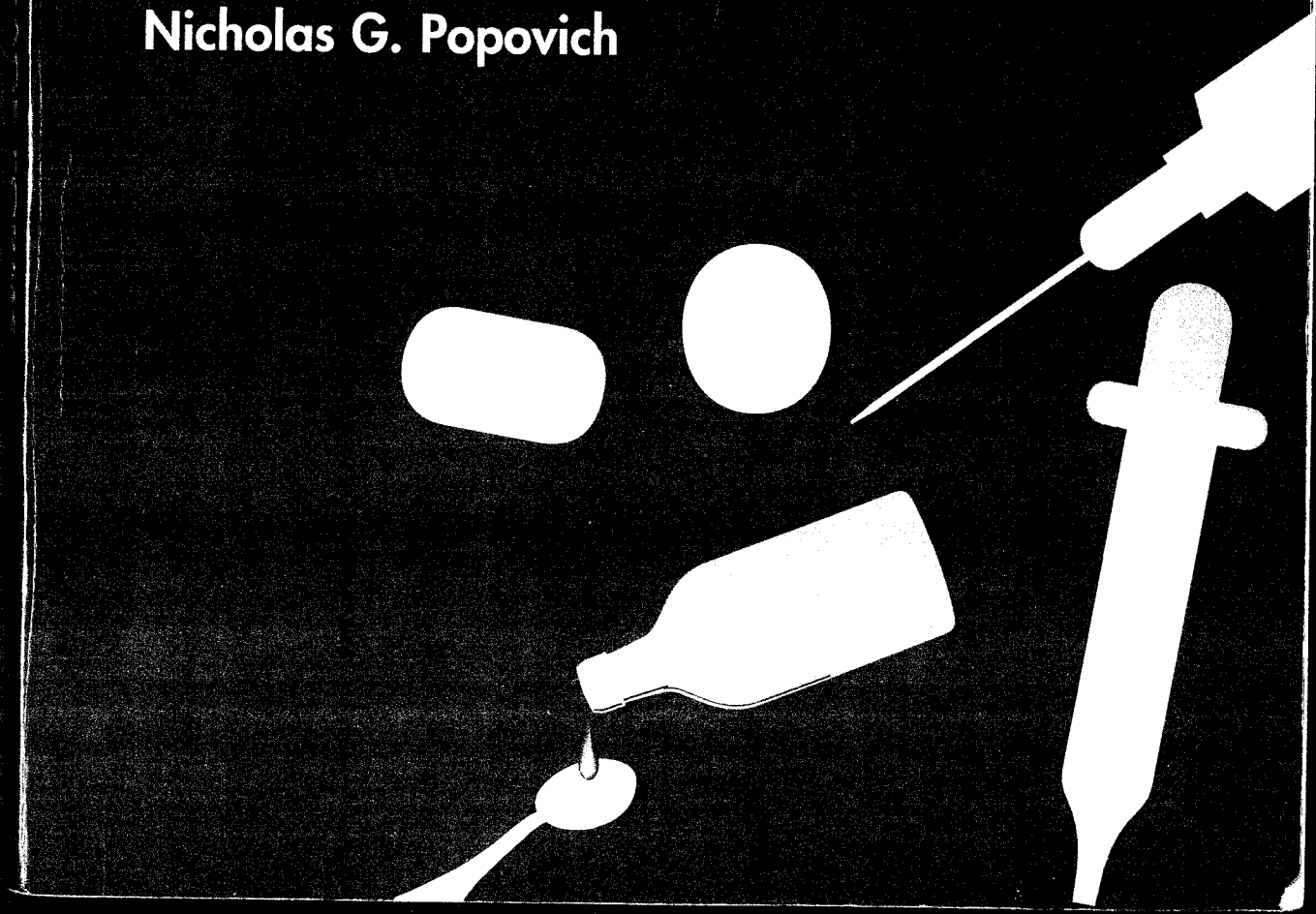

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pensions, can interrupt the normal flow of blood within the circulatory system, and their use is generally restricted to other than intravenous administration. The onset and duration of action of a drug may be somewhat controlled by the chemical form of the drug used, the physical state of the injection (solution or suspension), and the vehicle employed. Drugs that are very soluble in body fluids generally have the most rapid absorption and onset of action. Thus, drugs in aqueous solution have a more rapid onset of action than do drugs in oleaginous solution. Drugs in aqueous suspension are also more rapid acting than drugs in oleaginous suspension due to the greater miscibility of the aqueous preparation with the body fluids after injection and the subsequent more rapid contact of the drug particles with the body fluids. Oftentimes more prolonged drug action is desired to reduce the necessity of frequently repeated injections. These long-acting types of injections are commonly referred to as repository or "depot" types of preparations.

The solutions and suspensions of drugs intended for injection are prepared in the same general manner as was discussed previously in this text for solutions (Chapter 12) and disperse systems (Chapter 13), with the following differences:

1. Solvents or vehicles used must meet special purity and other standards assuring their safety by injection.
2. The use of added substances, as buffers, stabilizers, and antimicrobial preservatives, fall under specific guidelines of use and are restricted in certain parenteral products. The use of coloring agents is strictly prohibited.
3. Parenteral products are always sterilized and meet sterility standards and must be pyrogen-free.
4. Parenteral solutions must meet compendial standards for particulate matter.
5. Parenteral products must be prepared in environmentally controlled areas, under strict sanitation standards, and by personnel specially trained and clothed to maintain the sanitation standards.
6. Parenteral products are packaged in special hermetic containers of specific and high quality. Special quality control procedures are utilized to ensure their hermetic seal and sterile condition.
7. Each container of an injection is filled to a volume in slight excess of the labeled "size" or volume to be withdrawn. This overfill permits the ease of withdrawal and administration of the labeled volumes.
8. There are restrictions over the volume of injection permitted in multiple-dose containers and also a limitation over the types of containers (single-dose or multiple-dose) which may be used for certain injections.
9. Specific labeling regulations apply to injections.
10. Sterile powders intended for solution or suspension immediately prior to injection are frequently packaged as *lyophilized* or freeze-dried powders to permit ease of solution or suspension upon the addition of the solvent or vehicle.

Solvents and Vehicles for Injections

The most frequently used solvent in the large-scale manufacturer of injections is *Water for Injection, USP.* This water is purified by distillation or by reverse osmosis and meets the same standards for the presence of total solids as does *Purified Water, USP,* not more than 1 mg per 100 mL Water for Injection, USP and may not contain added substances. Although water for injection is not required to be sterile, it must be pyrogen-free. The water is intended to be used in the manufacture of injectable products which are to be sterilized after their preparation. Water for injection should be stored in tight containers at temperatures below or above the range in which microbial growth occurs. Water for injection is intended to be used within 24 hours following its collection. Naturally, the water should be collected in sterile and pyrogen-free containers. The containers are usually glass or glass-lined.

Sterile Water for Injection, USP is water for injection which has been sterilized and packaged in single-dose containers of not greater than 1-liter size. As water for injection, it must be pyrogen-free and may not contain an antimicrobial agent or other added substance. This water may contain a slightly greater amount of total solids than water for injection due to the leaching of solids from the glass-lined tanks during the sterilization process. This water is intended to be used as a solvent, vehicle or diluent for already-sterilized and packaged injectable medications. The one-liter bottles cannot be administered intravenously because they have no tonicity. Thus, they are used for reconstitution of multiple antibiotics. In use, the water is aseptically added to the vial of medication to prepare the desired injection. For instance, a suitable injection may be prepared from the dry powder, Sterile Ampicillin Sodium, USP, by the aseptic addition of sterile water for injection.

Bacteriostatic Water for Injection, USP is sterile water for injection containing one or more suitable